a) a top backing layer that is impermeable to the drug;

b) a cast pressure-sensitive silicone adhesive layer which is contiguous to and underlies the backing layer, which contains said drug, and which is a source of the drug for the patch;

c) a solid pressure-sensitive acrylic adhesive layer which is contiguous to and which underlies and is in diffusional contact with said silicone adhesive layer; and

d) a removable release liner underlying the acrylic adhesive layer;

wherein the amount of drug in the patch is sufficient to provide a therapeutically effective amount of drug to the patient.

REMARKS

Reconsideration of the patentability of applicants' claims is requested respectfully.

Status of the Claims

The Examiner's Action addresses all of applicants' elected claims, namely Claims 1, 3, 6 and 7. Claim 1 has been amended. No claims have been cancelled. Claim 27 has been added. Accordingly, there is presented for Examiner's consideration Claims 1, 3, 6, 7, and 27.

Pursuant to the Examiner's Restriction Requirement of March 1, 2001 and applicants' Request for Reconsideration and Withdrawal of the Requirement, as set forth in applicants' Request of August 1, 2001, the Examiner has withdrawn from consideration Claims 2, 4, 5 and 8 to 26 as being drawn to a non-elected invention.

Summary of the Examiner's Rejections

Claim 1 has been rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 6,264,977 to Hoffmann (hereinafter "the Hoffmann reference").

Claims 1, 3, 6 and 7 have been rejected under 35 U.S.C. § 103 (a) as being obvious over:

(A) the disclosure of the aforementioned Hoffman reference;

(B) the disclosure of U.S. Patent No. 5,316,759 to Rose et al. (hereinafter "the Rose et al. reference"); or

(C) the combined disclosures of the Hoffmann reference and the Rose et al. reference (it is not clear from the Action which reference is considered to be the primary reference and which the secondary reference).

The Examiner's Section 103 rejection relies also on the knowledge of one of ordinary skill in the art and the disclosures of U.S. Patent Nos. 5,656,286 to Miranda et al. (hereinafter "the Miranda et al. reference") and 5,721,257 to Baker et al. (hereinafter "the Baker et al. reference").

Reconsideration of the Examiner's rejections is requested respectfully.

Summary of Applicants' Invention

Applicants' invention relates to a transdermal patch for delivering a drug which is normally a volatile liquid. The patch comprises: (A) a top backing layer that is impermeable to the drug; (B) a solid adhesive matrix which underlies the backing layer and which contains the drug; and (C) a removable release liner layer

which underlies and is adhered to the matrix. An example of the present invention is a transdermal patch for delivering nicotine which is a normally volatile material (see the present application page 3, lines 25 to 30). The nicotine is contained in the solid adhesive matrix which comprises multiple layers, as set forth in applicants' claims. A first solid layer comprises a silicone adhesive and a second solid layer underlies the first layer and comprises an acrylic adhesive which overlies the release liner. The nature of the properties of the solid layers of silicone adhesive and acrylic adhesive and their position in the patch relative to each other are important aspects of the present invention with regard to both the effectiveness of its use and the manufacture of the patch.

The use of the silicone adhesive is important because, among adhesives, silicone adhesives are highly soluble in high vapor pressure solvents, that is, solvents which vaporize readily. (Hexane is an example of such a solvent.). Such solubility properties of the silicone adhesive permit the use of a high vapor-pressure solvent which evaporates readily at a relatively low temperature, that is, at a temperature at which loss of the volatile drug is minimized or avoided during the drying process which results in the formation of the solid layer of the drug-containing silicone adhesive. In contrast, the use of an adhesive (as the drug-containing adhesive) which is not highly soluble in a high vapor-pressure solvent and which requires the use of a solvent that has a relatively low vapor pressure (thus, requiring the use of relatively high "evaporating" temperatures) would result in the loss of a substantial amount of the volatile drug during the manufacturing process.

Another important aspect of the use of the silicone and acrylic adhesives and their relative positions in the patch relates to the rate at which the drug is delivered from the patch to the surface of the skin. The nature of the two adhesives is that the

drug diffuses through a layer of the silicone adhesive at a faster rate than it diffuses through a layer of the acrylic adhesive. Accordingly, there is controlled diffusion of the drug from the layer of acrylic adhesive to the skin (see the present application, the paragraph bridging pages 5 and 6). The prolonged delivery of the drug into the body is a desirable feature of applicants' patch.

From the above description of applicants' invention, it should be appreciated that one of the important aspects of the invention is that the silicone adhesive layer of the patch is a source of the drug in the patch, that is, the patch, as made, includes a silicone adhesive layer which contains a supply of the drug. Applicants' independent Claim 1, as amended, and the additional claims that have been added to the application define also that the silicone adhesive layer is a source of the drug.

The discussion which follows shows clearly that none of the references of record discloses or renders obvious applicants' claimed patch. A summary of the disclosures of the references and, thereafter, a discussion of the Examiner's rejections are set forth below.

Summary of the Disclosures of the References

Each of the Hoffmann, Rose et. al., Miranda et. al., and Baker et. al. patents is summarized below.

U.S. Patent No. 6,264,977 to Hoffmann

The Hoffman reference discloses a transdermal patch comprising one or more solid or liquid drug sources (Col. 3, lines 10-12)) deposited in the form of a solid or a viscous liquid on the surface of a "matrix" layer (Col 5, lines 65-66), which can

comprise, for example, a silicone adhesive. Hoffman discloses that the matrix layer acts as a diffusion conduit which regulates the flux of the drug(s) which are deposited on the surface thereof as the drug(s) passes to the skin (Col. 3, lines 5-10). The Hoffman reference refers to the drug(s) deposited on the surface of the matrix layer as "active substance depots" (Col. 2, line 54). The Hoffmann reference discloses further that the patch is secured to the skin using the "matrix" layer itself (Col. 4, line 20-23) or optionally by means of a porous adhesive layer underlying the "matrix" layer (Col 5, line 45).

For the case of volatile drugs, the Hoffmann reference discloses injection of the volatile drug between two layers of the "matrix" materials placed one on top of the other (Col 6, lines 27-31). The Hoffmann patch does not disclose a silicone adhesive layer containing a drug and which is a source of drug for the patch. Also, the Hoffmann reference does not disclose the combination of a silicone adhesive layer which contains a drug and, in diffusional contact therewith, an acrylic adhesive layer.

U.S. Patent No. 5,316,759 to Rose et al.

The Rose et. al. reference discloses a transdermal patch in which the drug source is a liquid solution containing a drug or a neat liquid drug. In the Rose et. al. patch, the drug source is contained in a pouch formed by a liquid-impermeable backing layer and a liquid-permeable, skin-contacting layer which can comprise, for example, "...cotton material or a similar cloth-like material..." (Col. 8, lines 43-61). The Rose et al. reference discloses further that, in the case in which the drug source for the patch is a liquid drug solution, the solution can be contained in "micro-sealed compartments" (Col. 8, line 67 - Col. 9, line 2), as described in the

Sanvordeker et. al. patent (cited by Rose et al.). The Sanvordeker patent describes the compartments as a matrix of "...silicone rubber having from about 10 to 200 micron micro-sealed compartments being formed by in situ cross-linking of the silicone rubber after it is mixed with the hydrophilic solvent system containing ...[a drug]...and the hydrophobic solvent system" (Sanvordeker et al. Col. 3, lines 32-38). The disclosure of the Sanvordeker patent is summarized in Appendix A hereof.

The Rose et al. reference discloses further that "The exact details of the patch are not critical to the present invention ..." and cites U.S. Patent Nos. 3,731,683 and 3,797,494 both to Zaffaroni and 4,336,243 to Sanvordeker et al. as illustrative of the patches which can be utilized in the Rose et al. development. None of these patents discloses the transdermal patch of applicants' development. They are summarized in Appendix A hereof.

U.S. Patent No. 5,656,286 to Miranda et al.

The Miranda et al. (Miranda being an applicant herein) reference discloses a transdermal delivery device comprising an impermeable backing layer and a single layer comprising a blend of at least one adhesive, a poly(vinylpyrrolidone), and a drug. The Miranda et al. reference discloses further that drug flux delivered by the device is controlled by blending polymers into the single layer that have different solubilities for the drug contained in the layer. Although Miranda discloses a comparative composition comprising a silicone adhesive and a drug (nitroglycerine, estradiol, or pilocarpine) in Examples 6, 9, 15, 17, and 21, there is no disclosure respecting the combination of a silicone adhesive layer which contains a drug and, in diffusional contact therewith, an acrylic adhesive layer.

U.S. Patent No. 5,721,257 to Baker et al.

The Baker et al. reference discloses a transdermal patch comprising a nicotine-impermeable backing layer and a "monolithic" (that is, polymeric) layer containing nicotine (Col. 7, lines 58-60). The Baker et al. reference discloses further that the polymeric layer can comprise either an acrylic adhesive (Col. 9, line 32-36), a polyurethane polymer (Col. 9, lines 36-66) or an acrylate-based copolymer (Col. 10, lines 1-7).

The Baker et al. reference discloses further that, optionally, the polymeric layer may be affixed to the skin by a silicone adhesive layer underlying the patch (Col.10, line 17-33) and, optionally, by a urethane foam tape adhesive which serves to aid in regulating the flux of the drug delivered (Col 13, lines 11-16). The Baker et al. reference does not disclose a drug-containing layer of silicone adhesive which is a source of drug for the patch nor the combination of a silicone adhesive layer which contains a drug and, in diffusional contact therewith, an underlying acrylic adhesive layer.

Discussion of the Examiner's Rejections

Each of the Examiner's § 102 and § 103 rejections is traversed repectfully.

The Section 102 Rejection Based on the Hoffman Reference

Each of applicants' independent patch claims defines a patch in which the silicone adhesive layer is a source of the drug which is contained within the patch. The Hoffmann reference describes a drug-containing patch having one or more layers, one or more of which may comprise a silicone adhesive. However, none of the layers of the Hoffmann patch constitutes a source of the drug in the patch. The

source of the drug in the Hoffmann patch is a "depot" which is deposited on the surface of a layer of adhesive, (Col 6, lines 27-31 and Examples 1 and 2) and it is from this source that the drug flows through the underlying layers. The Hoffmann reference fails, therefore, to anticipate applicants' claims in that they define that the silicone adhesive layer constitutes a source of the drug - a feature not described in the Hoffmann reference.

Withdrawal of Examiner's § 102 (e) rejection is requested respectfully.

The Section 103 Rejection Based on the Hoffmann Reference

As discussed above, applicants' independent claims distinguish over the disclosure of the Hoffmann reference in defining a patch which comprises a solid silicone adhesive layer that is a source of the drug (a normally volatile liquid) in applicants' patch. There is absolutely no disclosure in the Hoffmann reference that would lead one skilled in the art to modify the patch described therein to include a silicone adhesive layer which contains and is a source of the drug in the patch. In fact, the Hoffmann reference teaches explicitly away from the structure of applicants' claimed patch in stating "...it is an advantage of the invention that...volatile substances...can be introduced...in the form of a depot, that is, liquid drug,...[t] here is no need for...mixing the reservoir matrix material for example, a silicone adhesive with the active substance that is, a drug" (underlined words added).

Accordingly, the Section 103 Rejection based on the disclosure of the Hoffmann reference should be a withdrawn because the disclosure leads one away from applicants' claimed patch.

Section 103 Rejection Based on the Rose et al. Reference

The Rose et al. reference discloses a patch for transdermal administration of nicotine and/or mecamylamine utilizing multiple porous layers (Col. 8, lines 43 - 58) through which a liquid solution containing the drugs is contacted to a site of administration. Rose et al. disclose a liquid drug source contained in either a cavity formed between patch layers or contained in interconnected voids permeating a non-adhesive silicone rubber mass (Col. 8, line 67 - Col. 9, line 2). Rose et al. disclose no single structural or functional feature that corresponds to a structural or functional feature of applicants' development. Specifically, Rose et al. do not disclose a silicone adhesive layer which contains a source of the drug in applicants' patch and an underlying acrylic adhesive layer which is in diffusional contact with the silicone adhesive layer.

The Section 103 Rejection Based on Combined Disclosures of Hoffman and Rose et al. and the Level of Oridinary Skill in the Art

As discussed above, applicants' independent claims define a patch which comprises a silicone adhesive layer which contains a drug and which is a source of the drug in applicants' patch. It has been pointed out above that Hoffman teaches away from applicants' invention and that Rose et al. describe a patch which does not include a silicone adhesive layer which contains and is a source of the drug in the Rose et al. patch and an underlying acrylic adhesive layer which is in diffusional contact with the overlying silicone adhesive layer.

Neither the Baker et al. nor Miranda et al. references describes a patch which includes, as a source of the drug in the patch, a drug-containing silicone adhesive layer in combination with an underlying acrylic adhesive layer which is in drug-diffusional contact with the overlying silicone adhesive layer.

Accordingly, it is submitted that applicants patch is not obvious over the combined disclosures of the references.

Submitted herewith are two pages entitled "Version with Markings to Show Claim Changes Made" and a Petition for Extension of Time to Respond to the Examiner's Action.

Respectfully submitted,
Synnestvedt & Lechner

March 15, 2002
Date

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1. (Once Amended) A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) an intermediate solid silicone adhesive layer which underlies the backing layer, which contains the drug and is a source in the patch of the drug [containing the drug and underlying] the backing layer;

c) [an] a solid acrylic adhesive layer [also containing the drug that] which underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer,

wherein the [combined] amount of drug in the patch [silicone adhesive layer and acrylic adhesive layer] is sufficient to provide a therapeutically effective amount of drug to the patient.

27. (New Claim) A transdermal patch for administering volatile liquid drugs transdermally comprising:

a) a top backing layer that is impermeable to the drug;

b) a cast pressure-sensitive silicone adhesive layer which is contiguous to and underlies the backing layer, which contains said drug, and which is a source of the drug for the patch;

c) a solid pressure-sensitive acrylic adhesive layer which is contiguous to and which underlies and is in diffusional contact with said silicone adhesive layer; and

d) a removable release liner underlying the acrylic adhesive layer;

wherein the amount of drug in the patch is sufficient to provide a therapeutically effective amount of drug to the patient.

Summary of Patents Cited in U.S. Patent No. 5,316,759 to Rose et. al.

U. S. Patent 3,731,683 to Zaffaroni

U. S. Patent No. 3,731,683 to Zaffaroni (hereinafter, "the '683 patent") discloses a "bandage" for providing topical medicaments to the skin to effect local treatment comprising a backing layer, a drug-containing "reservoir" underlying the backing layer, and a pressure-sensitive adhesive layer underlying the "reservoir" (Col. 2, lines 23 - 37). The "reservoir" comprises either a capsule or polymer matrix containing a drug. The matrix or capsule are made of a cured polymer. Suitable polymers can be, for example hydrophobic polymers, for example, silicone rubber, and hydrophilic polymers, for example, acrylic-based polymers. When the "reservoir" is a polymer matrix, it is formed by curing a solution of the polymer and a drug mixed therein to produce a solid polymeric mass with regions of the medicament interpenetrating it. The '683 patent discloses further that for either type of reservoir, the rate at which medicament can diffuse through the cross-linked polymer controls the rate at which medicament is administered to the skin to which the "bandage" is applied (Col. 5, line43-48). The '683 patent discloses further that a separate diffusion barrier may be optionally provided to regulate the flux of medicament provided. The diffussion barrier is made from the same polymers used to make the drug reservoir.

The '683 patent discloses that the devices may be secured to a section of skin receiving medicament by a layer of pressure sensitive adhesive applied to the exposed

face of the reservoir. The form of pressure sensitive adhesive is not specified but Example 3 discloses an acrylic-based pressure sensitive adhesive. The '683 patent does not disclose the use of a silicone adhesive layer which contains a drug and is a source of the drug in the patch, nor does it disclose, in diffusional contact therewith, an underlying acrylic adhesive layer.

U. S. Patent 3,797,494 to Zaffaroni

U. S. Patent 3,797,494 to Zaffaroni (hereinafter, "the '494 patent") discloses a bandage for providing topical medicaments to skin or mucosa to effect local treatment, the bandage comprising a reservoir containing a medicament which is made from a micro-porous material that regulates the release rate of the medicament and which is affixed to the skin surface to be medicated by a pressure sensitive adhesive. In an alternative embodiment, the '494 patent discloses a drug-containing reservoir of the type described above for the '683 patent; it additionally utilizes one or more micro-porous membranes between the reservoir and the skin to regulate the flux of medicament administered by the bandage. The '494 patent does not disclose the use of a silicone adhesive layer which contains a drug and is a source of the drug in the patch and, in diffusional contact therewith, an underlying acrylic adhesive layer.

U. S. Patent 4,336,243 to Sanvordeker et. al.

U. S. Patent 4,336,243 to Sanvordeker et. al. (hereinafter, "the '243 patent") discloses a "transdermal delivery pad"(i.e., a patch) for the transdermal administration

of nitroglycerine comprising a nitroglycerine impermeable backing layer and a layer comprising "...silicone rubber having from about 10 to 200 micron micro-sealed compartments being formed by in situ cross-linking of the silicone rubber after it is mixed with the hydrophilic solvent system containing ...[a drug]...and the hydrophobic solvent system" (Sanvordeker et. al. Col. 3, lines 32-38). The mass is formed by dissolving the drug in a solvent in which the silicone rubber is insoluble and blending it with a solution of the silicone rubber which is immiscible in the drug solution. The mixture of the two solutions is next subjected to a step which cross-links the silicone rubber, resulting in the silicone rubber mass described above. The '243 patent does not disclose the use of a silicone or acrylic adhesive layer in any capacity.

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